DETAILED ACTION

Amendment Entry

The amendment filed 21 March 2011 is acknowledged and has been entered. Claims 1-98 and 103 have been cancelled. Claims 108-118 are newly added. Claims 99-102 and 104-118 remain in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 99-102 and 104-118 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Selvais et al. (J. Cardiac Failure 6: 201, 2000), Selvais et al. (Eur. J. Clin. Invest. 28: 636, 1998), Hülsmann et al. (J. Am. Coll. Cardiol. 32: 1695, 1998), Rousseau et al. (Circulation 108 (17 Suppl.): IV-556, 2003), Berger et al. (J. Heart Lung Transplant. 22 : 1037, 2003), and Sabatine et al.

(Circulation 105: 1760, 2002) for reasons similar to those of record in the prior rejection of the similar subject matter of original claims 67-98.

Selvais et al. (2000) analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANF, i.e., N-proANP), brain natriuretic peptide (BNP), and endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes II-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and all 3, especially ET-1 and N-proANP levels, were significantly associated with death in these patients (see e.g. Table 3). Cut-offs were selected and used to determine, singly or in paired comparisons (see Tables 3 and 4, and Figs. 1 and 2), the risk of death in the patients, indicating low, intermediate, and high risk groups depending upon the number of markers elevated over the cut-offs (see especially Figs. 1 and 2). It is noted that the cut-off level of 1000 pg/ml selected for N-proANP is approximately 5.6 times the normal level of 178 pg/ml (see e.g. page 202). The reference teaches that clinically useful prognostic information can be easily obtained by measuring ET-1 and cardiac natriuretic peptide concentrations in patients with congestive heart failure (¶ bridging pages 205-206). The reference also suggests big ET-1 as a more stable and easier molecule to measure than ET-1 (see e.g. page 205, col. 1).

Selvais et al. (1998) analyzed the predictive value of plasma atrial natriuretic factor (ANF, i.e., ANP), N-proANP, and BNP for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and at least two of the peptides, N-proANP

and BNP levels, were significantly associated with death in these patients (see e.g. page 638). Cut-offs were selected and used to determine, singly or in paired comparisons (see Figs. 3 and 4), the risk of death in the patients, indicating low, intermediate, and high risk groups depending upon the number of markers elevated over the cut-offs (see especially Fig. 4).

Hülsmann et al. analyzed the predictive value of plasma atrial natriuretic peptide (ANP) and big endothelin-1 (ET-1) levels for survival in patients with congestive heart failure. A cut-off level of 4.3 fmol/ml of big endothelin-1, compared to normal levels of 0.8 to 1.8 fmol/ml (see page 1696, col. 2), provided short term prognostic event-free survival information (see e.g. page 1697 and Fig. 2). It is noted that the selected cut-off is 2.39-5.375 times the normal level range.

Rousseau et al. analyzed the predictive value of plasma N-ANP (1-25), N-ANP (68-98), BNP, N-BNP, ET-1, and big ET-1 for survival in patients with severe congestive heart failure (NYHA classes III-IV). All the measured analytes except BNP were found to significantly predict survival; however, both big ET-1 and ET-1 were strong independent predictors of survival in these patients. Cut-offs selected around the mean for big ET-1 ($\geq$ 12 pg/ml) and ET-1 (> 9 pg/ml) in the patients with severe congestive heart failure significantly predicted 5 year survival.

Berger et al. teach that endothelin and natriuretic peptides were known to have prognostic significance in chronic heart failure (CHF) and analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANP), N-terminal brain natriuretic peptide (N-proBNP), and big endothelin-1 (ET-1) for survival in patients with mild to

severe congestive heart failure (NYHA classes I-IV). The reference teaches that the different markers have different significance depending upon the clinical stage and the time of the observation period, big endothelin being best for predicting 1 year prognosis in patients with severe CHF and the natriuretic peptides, especially N-proANP, being better markers for 2-3 year prognosis in mild and moderate CHF, but the determinations of big endothelin and N-proANP were best for all patients. It is noted that in patients with severe CHF, the mean level of N-proANP was approximately 2.6 times the mean normal level (see e.g. Table II, Group C, value compared with normal value reported on page 1039).

Sabatine et al. teach that a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers enables clinicians to stratify risk for various prognoses, including death, in cardiac patients.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have determined various combinations of ET-1 and/or big ET-1 and/or cardiac natriuretic hormones and/or their fragments in the prediction of survival in patients with mild congestive heart failure because Selvais et al. (2000), Selvais et al. (1998), Hülsmann et al., and/or Berger et al., combined with the teachings of Rousseau et al., teach the well-known significance of these determinations, singly or in different combinations, for the prediction of survival in cardiac patients, those with congestive heart failure in particular, and Berger et al. teaches that determinations of the different peptide hormones provide complementary or different clinical information depending upon the severity of heart failure in the patient and the length of the

observation period, but in considering all patients, big endothelin and N-proANP were the best predictors, and Selvais et al. (2000) teach the determination of endothelin and N-proANP, but that big endothelin is more stable and easier to measure than ET-1, thereby specifically suggesting the determination of big endothelin and N-proANP. One of ordinary skill in the art would have been motivated to use the successful methods in combination in a method of prognosis prediction because determinations of these analytes had been taught individually or in the same combinations as instantly claimed or in different combinations by the prior art to be effective in the prediction of death in congestive heart failure patients and it would have been obvious to predict survival with multiple markers because the idea of doing so would have followed logically from their having been individually taught, as well as in the same or in other combinations, in the prior art to be useful for the same purpose, and, in particular, it would have been obvious to combine the determinations and individual cut-offs for each analyte in view of the direct suggestions in Selvais et al. (2000) and Selvais et al. (1998) to do so. Moreover, one would have had further obvious motivation to use a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers as taught in Sabatine et al. for the benefits taught therein. It would have been further obvious to one of ordinary skill to have followed the guidance provided in the combined teachings of the references to determine an optimal cut-off value in each particular assay, such as the specific cut-off range related to normal values taught in Hülsmann et al. for big endothelin or taught in Berger et al. for N-proANP, since it has been held that: where the general conditions of a claim are disclosed in the prior art,

discovering the optimum or workable ranges involves only routine skill in the art (see *In re Aller*, 105 USPQ 233); and, discovering an optimum value of a result effective variable involves only routine skill in the art (see *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 99-102 and 104-118 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Tsutamoto et al. (Eur. Heart J. 20: 1799, 1999), Berger et al. (J. Heart Lung Transplant. 22 : 1037, 2003), Selvais et al. (Eur. J. Clin. Invest. 28: 636, 1998), Selvais et al. (J. Cardiac Failure 6: 201, 2000), Rousseau et al. (Circulation 108 (17 Suppl.): IV-556, 2003), and Sabatine et al. (Circulation 105: 1760, 2002) for reasons of record in the prior rejection of the similar subject matter of original claims 67-98 re-instated herein below.

Tsutamoto et al. measured plasma levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and endothelin-1 (ET-1) in patients with New York Heart Association functional class I-II mild heart failure. The levels were compared to those in normals and used to determine the significance of the analyte levels as predictors of mortality in these patients. A cut-off level of BNP approximately 3.7 fold above the normal level (see e.g. pages 1800 and 1801-2) indicated significantly elevated mortality risk.

Berger et al. teach that endothelin and natriuretic peptides were known to have

prognostic significance in chronic heart failure (CHF) and analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANP), N-terminal brain natriuretic peptide (N-proBNP), and big endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). The reference teaches that the different markers have different significance depending upon the clinical stage and the time of the observation period, big endothelin being best for predicting 1 year prognosis in patients with severe CHF and the natriuretic peptides, especially N-proANP, being better markers for 2-3 year prognosis in mild and moderate CHF, but the determinations of big endothelin and N-proANP were best for all patients. It is noted that in patients with severe CHF, the mean level of N-proANP was approximately 2.6 times the mean normal level (see e.g. Table II, Group C, value compared with normal value reported on page 1039).

Selvais et al. (1998) analyzed the predictive value of plasma atrial natriuretic factor (ANF, i.e., ANP), N-proANP, and BNP for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and at least two of the peptides, N-proANP and BNP levels, were significantly associated with death in these patients (see e.g. page 638). Cut-offs were selected and used to determine, singly or in paired comparisons (see Figs. 3 and 4), the risk of death in the patients, indicating low, intermediate, and high risk groups depending upon the number of markers elevated over the cut-offs (see especially Fig. 4).

Selvais et al. (2000) analyzed the predictive value of plasma N-terminal atrial

natriuretic factor (N-proANF, i.e., N-proANP), brain natriuretic peptide (BNP), and endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes II-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and all 3, especially ET-1 and N-proANP levels, were significantly associated with death in these patients (see e.g. Table 3). Cut-offs were selected and used to determine, singly or in paired comparisons (see Tables 3 and 4 and Figs. 1 and 2), the risk of death in the patients, indicating low, intermediate, and high risk groups depending upon the number of markers elevated over the cut-offs (see especially Figs. 1 and 2). It is noted that the cut-off level of 1000 pg/ml selected for N-proANP is approximately 5.6 times the normal level of 178 pg/ml (see e.g. page 202). The reference teaches that clinically useful prognostic information can be easily obtained by measuring ET-1 and cardiac natriuretic peptide concentrations in patients with congestive heart failure (¶ bridging pages 205-206). The reference also suggests big ET-1 as a more stable and easier molecule to measure than ET-1 (see e.g. page 205, col. 1).

The teachings of Rousseau et al. are as set forth above in this Office action. The reference is cited as evidence that assays of N-terminal fragments (N-ANP (1-25), N-ANP (68-98)) of the N-terminal atrial natriuretic factor (N-proANP) provide predictive results similar to that provided by assays of the intact N-proANP known to the art such as those of Berger et al., Selvais et al. (1998), and/or Selvais et al. (2000).

Sabatine et al. teach that a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers enables clinicians to stratify

risk for various prognoses, including death, in cardiac patients.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have determined various combinations of ET-1 and/or big ET-1 and/or cardiac natriuretic hormones and/or their fragments in the prediction of survival in patients with mild congestive heart failure because Tsutamoto et al., Berger et al., Selvais et al. (1998), and/or Selvais et al. (2000), combined with the teachings of Rousseau et al., teach the well-known significance of these determinations, singly or in different combinations, for the prediction of survival in cardiac patients, those with congestive heart failure in particular, and Berger et al. teaches that determinations of the different peptide hormones provide complementary or different clinical information depending upon the severity of heart failure in the patient and the length of the observation period, but in considering all patients, big endothelin and N-proANP were the best predictors, and Selvais et al. (2000) teach the determination of endothelin and N-proANP, but that big endothelin is more stable and easier to measure than ET-1, thereby specifically suggesting the determination of big endothelin and N-proANP. One of ordinary skill in the art would have been motivated to use the successful methods in combination in a method of prognosis prediction because determinations of these analytes had been taught individually or in the same combinations as instantly claimed or in different combinations by the prior art to be effective in the prediction of death in mild congestive heart failure patients and it would have been obvious to predict survival with multiple markers because the idea of doing so would have followed logically from their having been individually taught, as well as in the same or in other combinations, in

the prior art to be useful for the same purpose, and, in particular, it would have been obvious to combine the determinations and individual cut-offs for each analyte in view of the direct suggestions in Selvais et al. (2000) and Selvais et al. (1998) to do so. Moreover, one would have had further obvious motivation to use a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers as taught in Sabatine et al. for the benefits taught therein. It would have been further obvious to one of ordinary skill to have followed the guidance provided in the combined teachings of the references to determine an optimal cut-off value in each particular assay, since it has been held that: where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (see *In re Aller*, 105 USPQ 233); and, discovering an optimum value of a result effective variable involves only routine skill in the art (see *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 21 March 2011 have been fully considered but they are not deemed to be persuasive.

Applicant's arguments with respect to the claims have been considered but are moot in view of the new or newly re-instated ground(s) of rejection. However,

applicant's arguments as applicable to these ground(s) of rejection are addressed herein below.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this regard, applicant urges that only Berger et al. specifically studies patients with mild heart failure. This is not found persuasive for the reasons of record and as set forth above in view of the teachings of Selvais et al. (2000), Selvais et al. (1998), Berger et al., and Hülsmann et al. or Tsutamoto et al. Also in this regard, applicant urges that none of the references teach determination of big endothelin and full-length N-proANP. This is not found persuasive for the reasons of record and as set forth above in view of the combined teachings of Selvais et al. (2000), Rousseau et al., Hülsmann et al., and Berger et al., and particularly in view of the teachings of Selvais et al. (2000) and Berger et al. Moreover, the argument is not found persuasive because many of the rejected claims do not require determination of big endothelin.

Notwithstanding applicant's assertions to the contrary, one of ordinary skill in the art would have appreciated that markers shown to be independent in multivariate analysis each provide unique complementary prognostic information that can be combined to provide an improved prognosis as clearly taught in the references such as

Selvais et al. (1998), Selvais et al. (2000), Berger et al., and Sabatine et al., and Hülsmann et al. or Tsutamoto et al.

Notwithstanding applicant's assertions to the contrary, the declaration of Dr. Gerhard Hawa under 37 CFR 1.132 filed 09 November 2010 is insufficient to overcome the rejections of the instant claims under 35 U.S.C. § 103(a) over the combined teachings of the references as set forth herein above because:

The declaration refers only to the system described in the above referenced application and not to the individual claims of the application. This is particularly evidenced by the focus of the declaration on differences between measurements of ET-1 and big ET-1 in severe and mild congestive heart failure when the claims are limited to measurement of full-length N-proANP in combination with BNP, N-proBNP, or big ET-1 in mild congestive heart failure. As such the declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. Moreover, the examiner did not suggest, as argued in the declaration, directly importing big endothelin-1 (ET-1) into the reference of Selvais et al. (2000) as a substitute for the determinations of endothelin-1 (ET-1) therein, because, for the reasons of record, the combined teachings of the references suggest that the determination of big endothelin and N-proANP should be performed because, inter alia, big endothelin is more stable and easier to measure than ET-1 as taught in Selvais et al. (2000), big ET-1 and ET-1 were strong independent predictors of 5 year survival in patients with congestive heart failure (albeit NYHA classes III-IV) as taught in Rousseau

et al., and determinations of big endothelin and N-proANP or ANP were best for predicting survival in all congestive heart failure patients as taught in Berger et al. or Hülsmann et al.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute in view of the new ground(s) of rejection necessitated by applicant's amendment set forth above.

Remarks

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ruskoaho (Endo. Rev. 24: 341, 2003) teaches that "because plasma ANP, N-ANP, BNP, and N-BNP levels are increased in proportion to the severity of left ventricular dysfunction and in parallel with the activation of other neurohormonal systems, the association of cardiac hormones with prognosis in patients with chronic heart failure is an expected finding" (see page 347, col. 2).

Valdemarsson et al. (J. Int. Med. 235: 595, 1994) analyzed the predictive value of plasma atrial natriuretic factor (ANP) for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV).

Clerico et al. (Horm. Metab. Res. 31: 487, 1999) teach that determining the plasma levels of ANP, BNP, and/or N-terminal-derived fragments of the prohormones provide complementary or different clinical information (see e.g. page 491, col. 1, last ¶). The reference teaches that in 1999 "the importance of measuring the circulating

levels of cardiac natriuretic hormones in . . . predicting mortality/survival rates is now well known" (see page 493, col. 2).

Asada et al. (US 6,828,107) teaches that levels of BNP in heart failure patients can be detected as increased several tens to several hundreds times that of healthy normal subjects (see e.g. col. 1).

Tsutamoto et al. (American J. Cardiol. 76: 803, 1995) teach that plasma endothelin-1 (ET-1) levels increased with the severity from mild to severe congestive heart failure (NYHA classes II-IV) (see e.g. page 805 and Fig. 2) and analyzed the predictive value of a plasma ET-1 cut-off level for survival in these patients (see e.g. page 806 and Fig. 6).

Stanek et al. (Trans. Proc. 29: 595, 1997) teach big ET-1 levels as a predictor of survival in NYHA class II-IV heart failure patients.

Buechler et al. (US 2004/0121343) teach multimarker panels for differential diagnosis.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR REPLY TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE MAILING DATE OF THIS ACTION.

IN THE EVENT A FIRST REPLY IS FILED WITHIN **TWO MONTHS** OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE **THREE-MONTH** SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR REPLY EXPIRE LATER THAN **SIX MONTHS** FROM THE MAILING DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 11 a.m. to 7 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, SPE, can be contacted at (571) 272-0806.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
June 6, 2011

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6/5/11